Research Article

Association of Homocysteine with Body Mass Index in Women with Polycystic Ovary Syndrome

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ABSTRACT

Objectives: Polycystic ovarian syndrome (PCOS) is a prevalent endocrine disorder that significantly impacts women. It is closely associated with metabolic syndrome and obesity. However, the exact interplay between serum homocysteine levels and body mass index (BMI) in PCOS patients remains incompletely understood. In this study, we investigated homocysteine levels in normal-weight and overweight/obese Iranian women with and without PCOS.

Methods: A total of 189 women with PCOS and 86 healthy fertile women were enrolled in the study. The patients and controls were divided according to BMI into two groups as follows: BMI < 25 kg/m² and BMI ≥ 25 kg/m². Blood samples were collected from all participants to assess fasting blood glucose, fasting insulin, lipid profile, free testosterone, and homocysteine levels.

Results: BMI, HOMA-IR, fasting insulin, total cholesterol (TC), LDL, and free testosterone levels were significantly elevated in the PCOS group compared with controls. Homocysteine levels were increased in both overweight/obese and normal-weight PCOS groups compared with controls. However, no significant difference was observed in homocysteine levels between overweight/obese and normal-weight PCOS groups.

Conclusion: This study demonstrated that homocysteine levels were notably elevated in women with PCOS, regardless of their BMI.

Keywords: Polycystic Ovarian Syndrome; Homocysteine; Body Mass Index; Obesity

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Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder affecting women during their reproductive years, with a prevalence estimated between 15–18% (1). Diagnosis of PCOS hinges on the identification of at least two of the following criteria: clinical and/or biochemical signs of hyperandrogenism, oligo- and/or anovulation, and polycystic ovarian morphology (2). PCOS is classified into four phenotypes based on the presence or absence of these features (1). Women with PCOS exhibit a higher prevalence of obesity, insulin resistance (IR), and metabolic syndrome, consequently increasing their risk of developing long-term health complications such as type 2 diabetes mellitus, endometrial cancer, and cardiovascular diseases (3). While a definitive cure for PCOS remains elusive, current treatment strategies focus on managing the presenting symptoms (4). Homocysteine (HCY) is a transient intermediate metabolite formed during the breakdown of the amino acid methionine. Its metabolic fate involves either remethylation back to methionine or trans-sulfuration to cystathionine and ultimately cysteine. Remethylation is primarily facilitated by the enzyme methylenetetrahydrofolate reductase (MTHFR), while cystathionine-beta-synthase (CBS) catalyzes the trans-sulfuration pathway (5). Consequently, any defect in the enzymes involved in these pathways can lead to elevated plasma HCY levels, a condition known as hyperhomocysteinemia.

Several studies have implicated HCY as a potent inducer of inflammation (6, 7). Evidence suggests its involvement in modulating inflammatory functions of endothelial cells at the level of gene expression (8). Hyperhomocysteinemia correlates with increased insulin resistance, blood pressure, and low-density lipoprotein (LDL) cholesterol levels (9, 10). Notably, hyperhomocysteinemia is now recognized as an independent risk factor for the development of chronic inflammatory diseases, including cardiovascular conditions and metabolic syndrome (11). Furthermore, research indicates elevated serum HCY levels in women with PCOS compared to control groups (12). This finding suggests a potential link between PCOS and HCY, warranting further investigation into the underlying mechanisms and potential clinical implications. Prior research on the association between HCY concentrations and obesity has yielded ambiguous results. While some studies observed significantly elevated HCY levels in obese individuals, others reported no such correlation (13, 14). Similar inconsistencies have been noted in studies investigating HCY levels in patients with PCOS (15). The present study aims to investigate HCY levels in both normal-weight and overweight/obese women with PCOS, compared with healthy controls among Iranian women.

Materials and methods

Study participants

This study represents a secondary analysis of previously published data (16–18). It employed a case-control design involving 189 women diagnosed with PCOS and 86 healthy controls, aged between 25–35 years. PCOS diagnosis was based on the 2003 Rotterdam criteria (1), which require the presence of at least two of the following features: polycystic ovaries on ultrasound, clinical and/or biochemical signs of hyperandrogenism, and oligo- or anovulation (oligo-amenorrhea). Women with hyperprolactinemia, thyroid disorders, premature ovarian failure, congenital adrenal hyperplasia, Cushing's syndrome, or adrenal tumors were excluded. Participants who had used any of the following medications within the past three months—anti-hypertensives, weight-loss agents, anti-inflammatories, l ipid-lowering drugs, insulin-sensitizers, antioxidant supplements, or oral contraceptives—were also excluded. The control group consisted of women with regular menstrual cycles and no clinical or biochemical evidence of hyperandrogenism. Ethical approval for this study was obtained from the Ethical Committee of Tehran University of Medical Sciences, Tehran, Iran, and written informed consent was signed by all participants. Subjects were recruited from the Ibn Sina Infertility Center in Tehran, with controls selected from individuals undergoing routine laboratory checkups at the same center.

Anthropometrics and biochemical measurements

Anthropometric measurements were recorded for all participants. BMI was calculated using the standard formula: weight (kg) divided by height squared (m^2). Following a 10-hour overnight fast, 5 mL of venous blood was collected during the follicular phase of the menstrual cycle, as previously described (17, 19). Serum samples were immediately centrifuged (1,000 × g for 15 minutes), aliquoted, and stored at −80°C. Biochemical assessments included fasting blood glucose (FBG), lipid profile, HCY, fasting insulin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and free testosterone (FT), all measured according to previously published protocols (16–19). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the formula: HOMA-IR = ([FBG (mg/dL)] × [fasting insulin (μU/mL)]) / 405 (20).

Statistical analysis

All statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test, and skewed variables were logarithmically transformed to approximate a normal distribution. Normally distributed variables were presented as

Table 1. Clinical features of the study population

Variables	Non-PCOS (n = 86)	PCOS (n = 189)	p-value
Age (years)	29.76±4.28	29.77±4.10	0.993
BMI (Kg/m^2)	24.9(22.3-27.5)	25.66(23.55-28.73)	0.016
FBG (mg/dL)	90.5(84.00-97)	89(83.50-95)	0.449
Fasting Insulin (µU/mL)	2.68(1.94-3.79)	4.10(4.1-6.93)	<0.001
HOMA-IR	0.58(0.4-0.84)	0.86(0.6-1.57)	<0.001
TG (mg/dL)	115(92.75-151)	120.55(92.25-162.75)	0.305
TC (mg/dL)	162.16±39.93	175.07±36.11	0.008
LDL-C (mg/dL)	95(75-16.50)	98.5(78.25-119.90)	0.002
HDL-C (mg/dL)	46.5(42-52)	44 (39-49)	0.355
Free Testosterone (pg/mL) $^{\Delta}$	1.48(1.28-1.76)	3.13(2.45-3.911)	<0.001
HomoCys (µU/L)	10.22(8- 12.72)	11.51(9.2-15.01)	0.003

Parametric variables are reported as mean ± standard deviation and non-parametric variables as median (IQR).

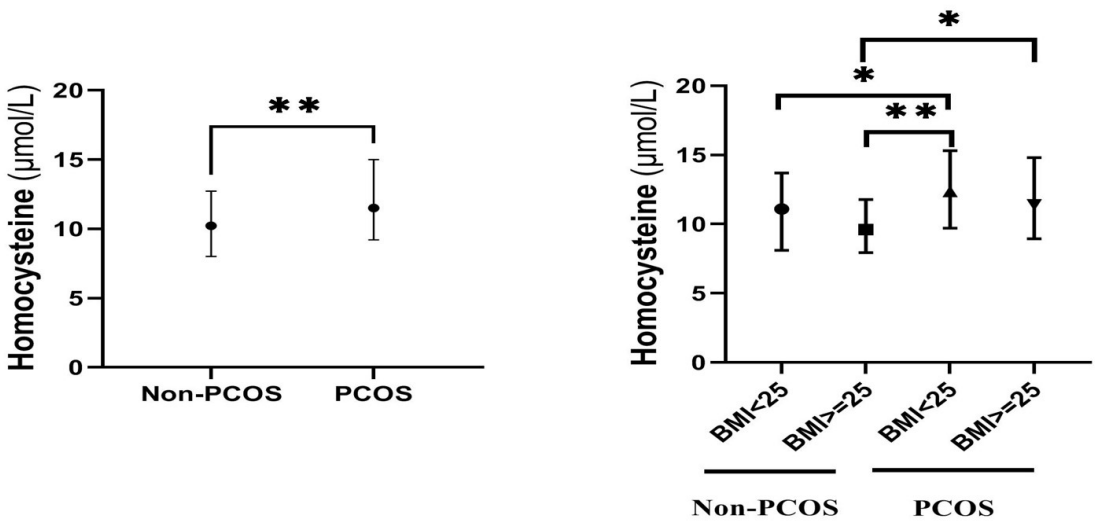

Figure 1. Serum levels of HomoCys in PCOS and non-PCOS women with normal weight and overweight/obese. Comparison was made using student t test and one-way ANOVA supplemented with Bonferroni test.

means with standard deviations (SD). Between-group comparisons (PCOS vs. non-PCOS) for normally distributed variables were conducted using Student's t-test. Both PCOS and non-PCOS groups were further stratified by BMI into normal weight (BMI < 25 kg/m²) and overweight/obese (BMI ≥ 25 kg/m²) categories, and compared using one-way ANOVA, supplemented with Bonferroni post hoc tests. A p-value less than 0.05 was considered statistically significant.

Results

The clinical characteristics of the study population in both PCOS and non-PCOS groups are presented in Table 1, as reported in previous studies (16–19). A statistically significant difference was observed in BMI between the PCOS and non-PCOS groups. Levels of fasting insulin and HOMA-IR were significantly higher in the PCOS group compared to the non-PCOS group (P < 0.001). Additionally, the PCOS group demonstrated elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and free testosterone (FT) relative to controls. No significant differences were found in fasting blood glucose (FBG), triglycerides (TG), or high-density lipoprotein cholesterol (HDL-C) between the two groups.

As shown in Table 1 and Figure 1, circulating HCY concentrations (µU/L) were significantly higher in the PCOS group compared to the non-PCOS group (P < 0.001).

Table 2 outlines the clinical and laboratory characteristics of participants stratified by BMI: normal weight (BMI < 25 kg/m²) and overweight/obese (BMI ≥ 25 kg/m²). HCY levels were significantly higher in both normal-weight and overweight/obese PCOS subgroups (12.35 and 11.39 µU/L, respectively) compared to their respective control subgroups (11.09 and 9.61 µU/L, respectively). Furthermore, HCY concentrations were significantly higher in normal-weight PCOS women than in overweight/obese non-PCOS women (Figure 1). However, no significant association was found between HCY levels in overweight/obese versus normal-weight PCOS groups. HOMA-IR and fasting insulin levels were significantly elevated in both PCOS subgroups (normal-weight and overweight/obese) compared to controls (P < 0.001). HDL-C levels were significantly lower in overweight/

Table 2. Clinical and laboratory parameters of normal weight and overweight/obese women with or without PCOS.

Parameters	Non-PCOS		PCOS		p-value
	BMI <25	BMI ≥25	BMI <25	BMI ≥25	
Age (years)	29.13±4.24	30.42±4.27	29.53±4.14	29.93±4.09	0.475
BMI (Kg/m^2)	22.55 (21.30_24.07)	27.6 (25.67_29.3)	23.23 (22.05_24.19)	28.12 (26.17_29.75)	
FBG (mg/dL)	88 (84.25_94)	94 (83.50_100.75)	88 (84_94)	89 (83_97)	0.354
Fasting Insulin (µU/mL)	2.37^{abc} (1.64_3.14)	3.15^{ae} (2.13_4.64)	3.85^{b} (2.56_6.14)	4.31^{ce} (2.89_7.3)	<0.001
HOMA-IR	0.52^{abc}(0.33_0.67)	0.65^{ae}(0.46_1.17)	0.83^{b}(0.55_1.24)	0.94^{ce}(0.61_1.68)	<0.001
TG (mg/dL)	118.5 (88.25_143.75)	111.5 (96.20_155.25)	109 (81_162.5)	127 (100_164)	0.121
TC (mg/dL)	159.22^{a} ±34.00	165.24±45.54	172.03±37.89	177.16^{a} ±34.85	0.039
LDL-C (mg/dL)	95 (95_115.75)	94.5 (74.75_117)	93 (75_121.4)	101(85_119.75)	0.374
HDL-C (mg/dL)	48^{c}(43.25_52.75)	45^{e} (41_51.25)	46 (39_52)	43^{ce}(38_47)	0.001
Free Testosterone (pg/mL)	1.48^{bc}(1.26_1.81)	1.49^{de}(1.29_1.70)	3.13^{bd}(2.54_3.90)	3.13^{ce}(2.36_3.94)	<0.001
HomoCys (µU/L)	11.09^{b}(8.11_13.69)	9.61^{de}(7.94_11.78)	12.35^{db}(9.70_15.30)	11.39^{e}(8.93_14.80)	<0.001

Groups with the same uppercase letter are significantly different according to Bonferroni's post hoc test. $P < 0.05$ is statistically significant.
PCOS: Polycystic ovary syndrome; BMI: Body mass index; FBG: Fasting blood glucose; TG: Triglyceride; TC: Total cholesterol; LDL-C: Low density-lipoprotein cholesterol; HDL-C: High density-lipoprotein cholesterol

obese PCOS participants compared to both normal-weight and overweight/obese controls ($P < 0.001$). Free testosterone levels were significantly higher in both normal-weight and overweight/obese PCOS subgroups than in their respective non-PCOS counterparts ($P < 0.001$).

Discussion

Elevated levels of HCY, a condition known as hyperhomocysteinemia, have been linked to various inflammatory diseases (21). The mechanisms underlying the connection between HCY and inflammation are not fully understood. However, it is hypothesized that HCY may induce inflammation through mechanisms such as oxidative stress, endothelial dysfunction, and activation of the nuclear factor-kappa B (NF-κB) signaling pathway (21, 22).

Although the exact cause of PCOS remains unknown, it is believed to result from a combination of genetic and environmental factors (23). Increasing evidence suggests that inflammatory markers, such as HCY, may play a role in the pathogenesis of PCOS. Studies have demonstrated a positive correlation between HCY levels and inflammatory markers in women with PCOS. For example, a study by Xinyu et al. (24) found that HCY levels were significantly elevated in women with PCOS compared to controls, and positively correlated with markers such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Consistent with these findings, our results showed significantly higher HCY levels in PCOS women compared to the non-PCOS group. The relationship between HCY and PCOS remains a complex and evolving area of research. Further studies are warranted to explore the underlying mechanisms and potential therapeutic implications of targeting HCY or related inflammatory pathways in PCOS. Insulin resistance—affecting up to 70% of patients—is considered a central feature of PCOS pathophysiology and can lead to elevated androgen levels, further exacerbating PCOS symptoms (25). Interestingly, prior research suggests a positive correlation between plasma insulin and HCY levels in various clinical contexts (26). In this regard, elevated HCY levels have been shown to correlate significantly with insulin resistance and hyperinsulinemia in PCOS patients (27). While obesity is a known contributor to insulin resistance, the association between HCY and obesity in PCOS appears more complex. In our study, no significant correlation was found between BMI and HCY levels among women with PCOS. This finding aligns with the results of Rekha et al. (2013), who reported that obesity is not an independent risk factor for elevated HCY levels in PCOS patients (15). Conversely, a meta-analysis identified an association between HCY and obesity (13), and a study by Sadaria et al. found significantly higher HCY levels in obese PCOS patients compared to their non-obese counterparts (28). These discrepancies may stem from methodological differences, variations in study populations, and confounding factors such as diet, physical activity, and hormonal status.

In the current study, both normal-weight and overweight/obese PCOS groups exhibited significantly elevated fasting insulin and HOMA-IR levels compared to BMI-matched controls. However, no significant difference was observed between the obese and non-obese PCOS subgroups in terms of fasting insulin and HOMA-IR. These findings suggest that insulin resistance may be independent of BMI in women with PCOS, consistent with previous research (29).

Elevated androgen levels are commonly found in women with PCOS. However, given that 30%–50% of PCOS patients exhibit normal total testosterone levels (30, 31), serum free testosterone (32) has been proposed as a more appropriate marker for assessing hyperandrogenism. In

the present study, testosterone levels were significantly higher in both overweight/obese and normal-weight PCOS groups compared to controls, yet levels were comparable between obese and non-obese PCOS subgroups. In agreement with the study by Yasmin et al. (33), we did not observe any association between testosterone levels and BMI in women with PCOS.

This study has several limitations. The relatively small sample size may affect the generalizability of the findings. Furthermore, the study's focus on an Iranian population may limit applicability to other ethnic groups. Additional anthropometric measures such as waist-to-hip ratio (WHR), waist circumference (WC), or body composition analysis could have provided more comprehensive insights than BMI alone. Lastly, the study did not account for other variables that may influence HCY levels in PCOS, including physical activity, dietary habits, and hormonal status—factors that should be explored in future research.

Conclusion

The results of the present study indicate elevated HCY levels in PCOS women independent of BMI. This suggests that obesity may not be a key driver in the exacerbation of inflammatory markers, particularly HCY. However, further research is warranted to elucidate the complex interplay between HCY, obesity, and PCOS. Additionally, investigating the potential role of HCY management in PCOS treatment strategies could be a valuable avenue for future exploration.

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Conflict of interests

The authors declare no conflict of interest.

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